THE VETERINARY JOURNAL

Editor :
T. DALLING, M.A., M.R.C.V.S.

Sub-Editor :
PROFESSOR J. McCUNN, M.R.C.V.S., M.R.C.S., L.R.C.P.,
Professor of Anatomy, The Royal Veterinary College.

FEBRUARY, 1943

EDITORIAL

CHEMOTHERAPY

We publish in this issue of The Veterinary Journal articles on chemo-therapeutical agents. One is an instalment of a general article on the subject while the other is an account of a specific piece of work on the experimental evaluation of sulphanilamide in certain streptococcal infections of domestic animals. Much research work has followed the discovery of prontosil and its effects on hæmolytic streptococci *in vitro* and *in vivo*. We owe much to the efforts of the workers in chemistry who, by their patient researches, are preparing new compounds of marked therapeutic value in infectious disease control. The treatment of many bacterial infections has now been completely altered and the results leave no doubt of the value of the various agents. The rapidity with which the different chemo-therapeutic agents have been prepared and the short time between their introduction, testing for therapeutic value in the laboratory and their application in the field are quite remarkable. The result is that we have now at our command a variety of agents of proved value, which can be used with confidence in the different diseases for which they are suitable. New agents continue to appear; laboratory and field experiences soon show their value.

The toxicity of some of the agents has to be borne in mind as well as the fact that a certain agreed concentration in the blood-stream is necessary to ensure their usefulness. It follows, that they must be used in amounts and for conditions which experiments have shown to be suitable. There may be a tendency, for example, to reduce the recognised effective dose or to curtail the course of treatment, especially in livestock, with the result that the expected and desired result may not materialise. It is important, therefore, that veterinary surgeons become familiar with the effects produced by the various agents and appreciate the circumstances in which they can best be used.

The local application of some of the agents in injuries and wounds has been followed by spectacular results. Many of us can recall vividly the somewhat unsatisfactory method of treating wounds in horses during the last Great War

and the length of time during which the animals were out of action till the healing process was completed. Had some of the now commonly used chemotherapeutic agents been available in those days, our task would have been much simplified. Truly patient research work is altering our methods of treatment and the practical application of its results is of the greatest service in our daily work.

"THE JOURNAL OF COMPARATIVE PATHOLOGY AND THERAPEUTICS"

It was with deep regret that veterinary research workers in this country learned that the late Sir John M'Fadyean decided early in the course of the present war, in March, 1940, to suspend publication of his journal. With the return of less anxious conditions and the fortunate decision of authority to foster research into animal disease as an important item in our war-time economy, there has been felt among the growing body of veterinary research workers employed in this country the need for a journal corresponding to Sir John's journal. It is therefore with pleasure that we now notice its reissue under the editorship of a board of four veterinary workers (J. G. Wright, T. J. Bosworth, J. T. Edwards, R. E. Glover) to whom, we learn from a foreword, Sir John had confided his wishes in regard to the manner of continuance of the journal shortly before his death.

Founded in the year 1888, *The Journal of Comparative Pathology and Therapeutics* remained in the ownership and editorship of the late Sir John M'Fadyean for the unrivalled period of 52 years. In its pages are recorded some of the most important advances in modern veterinary science, not the least important of them being those announced by Sir John himself. It started shortly after the beginning of the bacteriological era, following the researches of Pasteur and Koch. The earliest attempts at the use in this country of such agents as tuberculin and mallein are recorded in it. Since those beginnings the field of veterinary science has greatly expanded in many different directions largely through the impact upon it of precious contributory aid from a number of advancing cognate sciences. The variety of articles in the first number depicts the range of specialisation in which it is now necessary to indulge to make any serious advance in veterinary science. The editors state that they need not attempt to define the present limitations of the field of veterinary science, even if it were possible to do so, but that they will be happy to receive papers for consideration which represent a serious contribution to the advancement of knowledge within the now much expanded field.

A pleasing feature of the reissue, and one which will bring back affectionate recollections to his many former pupils, is the reproduction of the small photograph on the front cover of Sir John in his later years.

General Articles

CHEMOTHERAPY

By Major HAMILTON KIRK

ACCORDING to the medical dictionaries, this is "a mode of treatment based on the selective affinity which various chemicals have for the tissues of the body and for organisms that may infect it." The drugs in question have an effect on the disease-producing organisms without causing harm to the body of the host.

Chemotherapy can, of course, have a wider meaning to include the use in medicine of any synthetic chemical compound. This would thereby include such products as synthetic hormones, vitamins, anthelmintics, antiseptics, etc.

But for the purpose of this treatise chemotherapy is restricted as meaning the treatment of infections (bacterial, protozoal or virus in origin) by means of synthetically prepared chemical compounds.

History. Very early, histological workers had observed that certain cells readily take up various dyestuffs whilst others do not. This observation suggested a search for substances which would attach themselves to infective organisms circulating in the blood, and, by mixing with their plasma, so influence them as to cause them to perish. The body of the host should, however, not be affected by these substances, the action of which should be a selective one.

Since Ehrlich's discovery of Salvarsan (which was first valued as a remedy against trypansomiasis, and since 1910 has been used chiefly against spirochætes) new chemotherapeutic remedies for protozoal diseases have appeared at regular intervals and have proved their worth.

In bacterial infections, however, the outlook was gloomy until the discovery of an azo-dyestuff (prontosil) by Mietszch and Klarer of the I.G. Farbenindustrie, and which Prof. Domagk[1] reported as possessing a specific effect against streptococcal infection in mice.

The first report on the use of this dark red dye was submitted to the therapeutic Trials Committee of the Medical Research Council, and appeared in the *Lancet*, June 6, 1936.

Late in 1935 it was found that this dyestuff was reduced in the body to a colourless compound—p-aminobenzenesulphonamide, which was simpler in composition and was regarded as responsible for the therapeutic effect. To this compound the non-proprietary name "sulphanilamide" was given, whilst the word "sulphonamide" was used to indicate the whole group of drugs.

In the years following, a great number of derivatives of sulphonamide were elaborated, but the one of outstanding importance was "sulphapyridine," popularly known as M & B 693. Excepting the latter, all of them were originally introduced for the treatment of human hæmolytic-streptococcal infections, and their use in similar infections of animals followed. The original and specific indication for sulphapyridine was against pneumococcal infections.

True chemotherapeutic agents may be divided into two classes:

(a) Those with an anti-bacterial action, such as the sulphonamides and allied substances;

(b) Those with an anti-protozoal activity, which would include Acaprin, Naganol, the diamidines, arsenicals, trypan blue, etc.

As far as virus infections are concerned, chemotherapy has not yet proved of any value.

The original idea that the action of these sulphonamide drugs was selective on certain organisms is now known to be erroneous. The various drugs of the group differ one from another only in their degree of activity, with the result that the more active compounds are capable of dealing with the more resistant organisms at lower concentrations than the less active drugs. For instance, sulphanilamide, although virtually valueless in practice in treating staphylococcal infections via the blood-stream, can inhibit the growth of *Staphy. aureus in vitro* if present in sufficient concentration.

Such concentrations cannot, of course, be obtained within the body of an animal; but therein lies one of the fundamental differences when sulphonamides are applied locally, as by topical application high local concentrations can be obtained consistent with the solubility of the drug.

In the laboratory, sulphanilamide, sulphapyridine and sulphathiazole can be placed in that order of ascending activity, but in therapeutic use other properties of the sulphonamide drugs influence their value, for example, their different physical and pharmacological characteristics.

Chemotherapeutics Having Anti-Bacterial Activity

Sulphanilamide (Streptocide, Prontosil Album, etc.)

It was impossible at first to state exactly how sulphanilamide worked, but it is now known that this and other derivatives of the sulphonamide drugs do not neutralise toxins, and do not stimulate either phagocytosis or antibody formation. It has been maintained that their action depends on interference with some bacterial enzyme reaction associated with nutritive substances necessary for the growth of the organism.(2) & (3)

It is now agreed that the primary action of the drugs is one of bacteriostasis, the rate of growth of the bacterial cells being reduced. When present in very high concentration under some conditions, the drugs may also exert a bactericidal effect.

In mouse infections the drug exerted a marked protective action only if the streptococci used had a high mouse virulence, that is, when the organisms had been repeatedly passaged through mice. There was a much less marked effect if organisms freshly isolated from human beings were used in the experiments.

A high degree of activity is recorded against streptococci of human origin (Lancefield's Group A) and against those of animal origin belonging to Lancefield's Group C. In dogs the common streptococcus is the Group C organism about which less experimental evidence is available.

Therapeutic uses. Sulphanilamide displays a selective chemotherapeutic action against streptococcal, and slightly against staphylococcal, diseases, not only therapeutically but prophylactically.

Such susceptible organisms are the common culprits in many disease conditions, thus the field of usefulness for this drug is extensive.

In general, the conditions most likely to respond satisfactorily to sulphanilamide and its prototypes are puerperal and post-abortion sepsis, tonsillitis, streptococcal pneumonia, otitis media and arthritis of streptococcal origin, and sepsis of various kinds following operations. Reduction of fever should be noted a few hours after the very first dose.

Hudson and Smith[4] have given sulphanilamide intraperitoneally, prophylactically and therapeutically in human cases of peritonitis and peritoneal contamination, in doses of 10-15 gram, with considerable success.

Wood[5] administered it per rectum. Both in medical and surgical cases this method causes fewer complications, and it gives prompt results in mucous colitis. Sulphapyridine cannot be given this way with satisfactory results.

Tolerance. There is no change in blood pressure or in cardiac function, even when very large doses are injected. The renal route is that by which the drug is excreted in all animals, but this does not give rise to diuresis. The red colour imparted to the urine after injections of Prontosil " soluble " is due to excretion of the dye and not to blood pigment.

The solution and the tablets are very well tolerated and set up no irritation; but a dose of 1 gram per kilo of body-weight is toxic for the cat. The writer has noticed that an ordinary domestic adult cat receiving one of the (7½ gr.) tablets three times daily soon exhibits vomition and anorexia.

Stableforth[6] showed that dogs could tolerate large doses of the drug; in fact, that no untoward results attended the administration of doses far in excess of those suggested for therapeutic purposes. But, as in the cat, doses approximating 1 gram per kgm. body-weight could produce alarming nervous symptoms some hour or two after ingestion, then gradually to subside.

Other recorded cases are those by Morris and Allison[7], when a blood concentration of 15 mgm. per 100 c.c. was achieved with a dose of 3.16 grains per lb. body-weight at four-hourly intervals, thus a 20 lb. dog received approximately 60 to 75 grains during the first 24 hours, the drug being given in gelatine capsules. After the first 24 to 48 hours the dose was reduced to 2½ grains per lb. body-weight, four-hourly.

Absorption of sulphanilamide from the digestive tract is rapid into all the tissues and fluids of the body, a variable proportion of it undergoing acetylation to an inactive form in the liver, in the majority of mammals with the exception of the dog, and, as previously stated, elimination is entirely and quickly effected by the kidneys. That is why its administration in large or repeated doses to animals suffering from kidney disease might be dangerous. Elimination would be retarded.

Dosage. Dosage of the drug is best expressed as the amount which will, on administration, maintain a concentration in the blood sufficient to control the disease. This is approximately 10 mg. per 100 c.c. of blood.

Modification may be necessary due to variation in the rate of excretion, this being accelerated by fluid intake, and retarded by impaired renal function.

The important points to remember are that:

(a) Early treatment is essential to success, as the drug appears to exert its maximum effect when invading organisms are not yet in great abundance, though are actively multiplying in the blood-stream; also

because more complete recovery may be expected when serious and advanced pathological changes are prevented.

(b) Initial doses should be large in order that the concentration mentioned above may be rapidly attained. This can occur inside of four hours.

(c) Repetition of doses at short intervals is indicated in order to maintain that concentration; then continue with a reduced dosage until the symptons commence to abate. In no other way can an acute infection be overcome.

These statements apply, in the main, to all other members of the sulphonamide group. Thus, a dog acutely ill, may receive of the soluble sulphonamide (e.g., Soluseptasine) from 5 to 15 c.c. of the 10 per cent. solution, parenterally, every eight hours. Cats would have 3 to 5 c.c.

Of the powdered drug, dogs may take at least 1 gm. per 10 lb. body-weight per os, as an initial dose, and subsequently half that amount three times a day. Cats may receive an initial dose of ½-gram, to be followed by ¼-gram three times daily. The preparation is generally supplied in tablet form, each tablet containing 0.50 gram. For cats, the tablets may be crushed, and the resultant powder mixed with margarine or dripping and smeared on the teeth.

It is of the utmost importance to avoid underdosage at the commencement of treatment, as this may lead to the organisms developing drug fastness, which can occur within a matter of hours with inadequate treatment and renders subsequent increase in dosage useless.

It is often stressed, in the literature of manufacturers, that it is inadvisable simultaneously to give any saline laxative containing sulphur, e.g., mag. sulph., or sodæ sulph., etc. The reason why this should be avoided is now established as being, not because the laxatives themselves contain sulphur (the sulphur in such compounds as magnesium sulphate is in an extremely stable linkage), but because the increased fluidity of the intestinal contents which follows the administration of a laxative, particularly a saline preparation, permits of increased bacterial fermentation in the bowel, with the formation of soluble sulphides and H_2S. When these are absorbed into the blood-stream in the presence of sulphanilamide, a reaction takes place with the hæmoglobin, with the production of sulphæmoglobinæmia. This, though not a fatal reaction, may have serious consequences, as it persists for some time, and, rendering the hæmoglobin incapable of oxygenation, it has the effect of an anæmia.

Prontosil.—The preparations of Prontosil in use at the present time are "Prontosil Soluble" for intramuscular injection and "Prontosil Album" for oral use. White Prontosil is the same chemical product as sulphanilamide, the latter being the active breakdown product of the former. *Prontosil Album* has largely replaced the original red tablet, being more pleasant to take and cheaper to produce. Dogs and cats receive from 3 to 22 grains (according to size) three or four times daily. If the daily dose is large it is best given in portions every five hours.

The five per cent. *Prontosil Soluble,* obtainable in 5 c.c. ampoules, is for parenteral administration, and the rapid absorption which occurs from intramuscular injection secures a therapeutic effect hardly inferior to that obtained by the intravenous route. Large amounts introduced intramuscularly cause some

pain, and they should therefore be divided. Large subcutaneous doses would be best distributed in different parts of the body to avoid tearing of the tissues. The best results are probably obtained from one or two daily injections, combined with the oral administration of tablets every four hours until symptoms abate.

BENZYL SULPHANILAMIDE (Proseptasine) is a white, odourless substance devoid of the unpleasantly bitter taste of sulphanilamide. It is only slightly soluble in water, and is undoubtedly less toxic than sulphanilamide, but its activity is also of a slightly lower order. For this reason its use has, to some extent, diminished in favour of later discoveries.

SOLUSEPTASINE is a sulphanilamide derivative but differs from Proseptasine in being readily soluble in water, the 10 per cent. solution being well tolerated by administration through any parenteral route. It is particularly effective against Beta hæmolytic streptococcal infections, also to some extent in mixed pyogenic infections, and in conditions due to coliform organisms. Thus it is widely used in the treatment of dogs and cats suffering from coliform cystitis, puerperal fever, metritis, peritonitis, pneumonia, otorrhœa and septic wounds, etc.

The dose of Soluseptasine is 3 to 10 c.c. (according to size of animal) repeated every eight hours whilst the symptoms remain acute.

Sulphapyridine (M & B 693—Dagenan)

World-wide attention has been directed to this sulphonamide on account of its outstanding success in combating human lobar pneumonia. It was soon shown, however, that this pneumococcal activity was not selective.

Sulphapyridine is a more active drug than sulphanilamide and consequently shows greater activity on a wider range of bacteria. In veterinary practice it has been tried out in a variety of infections and some success has been obtained in conditions previously resistant to treatment or in which sulphanilamide had only slight effect, e.g., calf pneumonia.

In the small-animal field attention naturally turned to the trial of sulphapyridine in canine distemper. At the request of the manufacturers the writer made careful tests with the drug in a series of susceptible puppies (experimentally infected with the distemper virus) and controls, and after trials occupying two to three months he was obliged to present an adverse report.

This inactivity of sulphapyridine on the virus of distemper has since been amply confirmed. In clinical cases of canine distemper, however, in which the secondary bacterial complications are predominant, some measure of success does appear to follow the use of the drug. A beneficial effect has been recorded particularly in pneumonias.[8]

It is now accepted that sulphapyridine has only relatively slight activity on *Staphylococcus aureus*, and although it has apparently proved of value in some clinical cases caused by this organism, there are now more active drugs available, such as sulphathiazole.

Sulphapyridine has a low solubility of approximately 1 in 4,000, on account of which its absorption from the alimentary tract tended (according to some observers) to be somewhat irregular and uncertain in some individuals compared with the absorption of sulphanilamide. There may be some truth, too, in the contention held by some, that, on account of this slower absorption, its concentration in the blood is much longer maintained. This is not yet definitely proved.

Dagenan sodium (or M & B 693 soluble) forms a highly alkaline solution in water and is therefore unsuitable for subcutaneous injection. The intravenous (preferably) or intramuscular routes are indicated for this product.

The initial dose of sulphapyridine for dogs under 20 lb. is ½ gm., ranging up to 2 gm. for those of 40 lb. and over; the subsequent doses, given three times a day, are from ¼ to 1 gm. Cats take ⅛ to ¼ gm. thrice daily.

The soluble preparation (Dagenan sodium) is more active and more toxic than the oral one, and the dosage is therefore lower. The average dose for dogs is 1 to 1½ c.c. (which are the equivalents of ⅓ to ½ gm. of Dagenan), which amounts may be given every eight hours intramuscularly or every six hours if given intravenously. For young animals the dose should be reduced according to age.

Sulphathiazole (Thiazamide—M & B 760)

Absorption and elimination are rather more rapid and toxicity is less than with sulphapyridine.

In human practice, staphylococcal septicæmia has a high mortality rate, yet Collins and Hardy[9] treated two cases with complete success, using sulphathiazole in massive doses orally. Both cases were gravely ill and the infection eventually became localised in a bone, in each case. A total amount of 232 gm. in one case and 169 gm. in the other was given, and the authors laid stress upon the fact that administration of the drug can be continued far beyond the limits usually regarded as constituting a fair therapeutic trial; and that the chance of success may actually be thrown away by setting an arbitrary limit to the dosage.

According to Province and Heath[10] sulphathiazole is a more desirable drug to take than sulphapyridine, as it causes less nausea, anorexia and vomiting. If these should occur, they state that Luminal is the best antidote. Of course, an ample administration of fluid also expedites elimination of the drug from the system.

In the opinion of the makers, the better tolerance and lower toxicity of this drug, in comparison with sulphapyridine, is of less practical importance in veterinary practice than in the treatment of human patients. The more rapid absorption and elimination, if found to be marked in the domestic animals, may be a drawback to the use of sulphathiazole, at least in any conditions for which sulphapyridine is almost equally satisfactory. It will no doubt, however, have a place in treating staphylococcal infections, and possibly some other bacterial infection.

Whilst we need not attach too much importance to any one of the many published reports on the use of sulphathiazole in human practice, it is fairly safe to say that the bulk of clinical reports do indicate that sulphathiazole has been responsible for a significant reduction in the mortality from staphylococcal septicæmia, although the death rate is still high. Only time and the experience gained from continuous clinical trial of this new drug upon animals will decide its usefulness to the veterinarian in combating this type of bacterial infection.

Sulphadiazine

This is the most recently introduced derivative and is still largely in the experimental stage. It is slightly less effective than sulphapyridine and sulphathiazole in the treatment of pneumonia, but is of definite value in cases of hæmolytic streptococcal and staphylococcal infections.

It occasions very little vomiting or nausea and is reported[11] to have been very successful in the tratment of meningococcic infections, sinusitis, and acute infections of the urinary tract due to *B. coli*.

It is less soluble in water than the other three members of the group, and smaller doses are required to maintain a given blood concentration, which, incidentally, may be reached in from two to four hours.

Nevertheless, it is readily absorbed from the intestinal tract and appears to be more slowly excreted, indicating that higher blood and tissue concentrations may be maintained.

An annotation[12] stated "that sulphadiazine had properties which, in a pharmacological sense, represented an immense advance. Higher blood levels were obtained with this drug than with any other sulphonamide compound, and were sustained longer, so that it evidently need not be given more often than six-hourly. The concentration in the blood plasma exceeds that in the blood cells—an advantage shared with sulphathiazole. On the other hand, where the latter is at some disadvantage, namely, in reaching the cerebro-spinal fluid in a concentration only one-third of that in the blood, sulphadiazine resembles sulphanilamide and sulphapyridine in attaining a concentration two-thirds of blood level."

"Tests of sulphadiazine on laboratory animals were made at the Johns Hopkins Hospital.[13] A high concentration of this compound was obtained in the blood of the rabbit after only one dose; and in chronic toxicity experiments, sulphadiazine produced less tissue damage in monkeys than either sulphathiazole or sulphapyridine. The percentage of survivals of mice infected with hæmolytic streptococcus and treated in each case with 10 mg. four times daily for three days with sulphanilamide, sulphapyridine, sulphathiazole and sulphadiazine was 25.71, 31.3, 3.75 and 51.5, respectively. In the treatment of streptococcal and pneumonic infections in mice, the results were also better than those obtained for the other three sulphonamides; and against infection with Friedlander's bacillus sulphadiazine gave a survival of 73.66 against less than 9 per cent. for the others." (*Pharm. Jnl.*)

Sulphaguanidine

This sulphonamide appears to be of especial value in the treatment of intestinal infections, particularly bacillary dysentery, avian coccidiosis, swine enteritis and "white scour" of calves. Its most remarkable property is its bactericidal action on the coliform organisms in the mouse intestine.

Although moderately soluble in water, the compound is very slowly absorbed from the intestinal tract, thus permitting the maintenance of a high concentration in the fæces whilst the blood concentration remains relatively low. The importance of maintaining a local concentration at the site of bacterial activity is obvious; but more clinical trial is needed before one can make any more detailed or authoritative statements.

Preliminary observations[14] made on the effects of feeding sulphaguanidine to chickens which were susceptible to cæcal coccidiosis, have shown that during such treatment they were wholly or partially protected against the disease.

Although there is as yet no direct evidence that sulphaguanidine has curative properties, treatment may prove of use in the control of an outbreak of coccidiosis among chickens.

The effect of this drug on specific feline enteritis has also to be investigated as early as possible.

Pyridium

An azo dye of the pyridine series is said to exert antiseptic properties for the urinary tract. It is claimed to have a selective action against various micrococci and the *B. Coli Com.*; and to be non-toxic, non-irritative, pain relieving, and equally effective in urine which is either alkaline or acid. Its clinical indications are cystitis, pyelonephritis, prostatitis, urethritis and

vaginitis, etc. It is contra-indicated in chronic glomerular nephritis, severe hepatitis and uræmia.

Pyridium is given orally in doses of 3 grs. (i.e., two tablets) three times daily before meals.

Yatren

Yatren is a chemotherapeutic with an iodine basis. A non-toxic, odourless powerful bactericide, having a property of deep penetration in consequence of the non-coagulation of albumen.

It is said to be specific against broncho-pneumonia, puerperal fever, bacillary white diarrhœa of fowls and paratyphoid of fur-bearing animals. It may be administered orally, parenterally or locally. Dose for dogs: One to four pills twice or thrice daily.

Uleron

A colourless sulphonamide compound chemotherapeutic for the treatment of staphylococcal or pneumococcal infections and well tolerated by animals.

Indicated for sinusitis, septic wounds, staphylococcal cystitis, pyelitis, and catarrhal sequelæ of distemper, in doses of ¼ to 3 tablets for dogs and cats, according to size, thrice daily for five days.

The writer has no practical knowledge of the last three preparations, and has found no published information concerning them. Their mention among this class of drugs is, however, probably justified on account of the wide publicity given to them in veterinary circles.

(To be concluded.)

SULPHANILAMIDE IN THE TREATMENT OF GROUP C AND GROUP G STREPTOCOCCUS INFECTIONS: MOUSE EXPERIMENTS

By A. W. STABLEFORTH,
Ministry of Agriculture and Fisheries, Veterinary Laboratory, Weybridge,
and
S. L. HIGNETT and R. W. ROACH,
Department of Agriculture, The University, Leeds

THE experiments* reported here were made in order to find whether sulphanilamide was likely to be effective in the treatment of group B, C, and G streptococcus infections respectively, and formed part of a wider investigation on the prospects of sulphanilamide treatment in animals. The fact that mouse infections with group C streptococci can be cured by means of sulphanilamide has already been reported (Stableforth, 1938) but publication of the experimental data was then postponed until observations on the other groups of streptococci had been made.

Long and Bliss (1939) quote Feinstone as having also found that sulphanilamide treatment was effective in mice inoculated with group C streptococci, whilst Descazeau, Courtade and Rocq (1939) reported protection by " para-aminophényl-sulfamide " (presumably sulphanilamide) against a virulent streptococcus isolated from a case of strangles.

Group C streptococci occur in various animals and are of considerable importance. In equines they account for nearly all wound infections, are con-

* Work done in the Division of Preventive Medicine, Royal Veterinary College, London.

cerned in strangles and most of the common respiratory infections, including pneumonia, and are also frequently present in certain abnormal conditions of the genital tract. They are also sometimes found in bovine mastitis, usually of the acute variety, in certain other sites in bovines, in dogs and sometimes in pigs, sheep and cats. Strangles strains correspond to the classical *Str. equi*, the others to the group which has been called *Str. pyogenes equi* (or *var. equi*) or "The animal pyogenes."

Group G streptococci occur mainly in dogs, being associated particularly with febrile throat and genital conditions and deaths in suckling puppies. They have also been found occasionally in cats, and once in a bovine udder (Stableforth, 1938).

Group B streptococci (*Str. agalactiæ*) occur regularly in the common chronic form of bovine mastitis.

Strains Used

The group C strains were K64 (Lancefield's group strain), S34 from a case of acute bovine mastitis, and GM17 from a case of endometritis in a mare. All were of the sub-group which ferments lactose and sorbitol, but not trehalose, i.e., the sub-group found in animal infections other than strangles. The group G strains were Price, from a case of pneumonia in a dog, and 18392 B & H, from puppies which died from a streptococcus septicæmia soon after birth.

Methods

A series of strains of the group required were passaged through mice and strains selected, of which only a few organisms, one or two to at most a few hundred, were need to kill mice.

A series of groups of mice, usually five for control groups and 20 for treated groups, were then given doses so chosen as to indicate whether protection occurred and, if so, the order of its effectiveness, i.e., whether against 10, 100, 1,000, or more times the average lethal dose, this dose being taken as the dose which killed about half the mice.

Cultures for inoculation were grown for 18 hours in blood broth and dilutions for counts and inoculations made in Ringer's solution. Deep blood agar plates were made in triplicate with 1 c.c. of the 10^{-5}, 10^{-6}, and 10^{-7} dilutions at approximately the same time as the mouse inoculations and colony counts made after 48 hours' incubation at 37 deg. Cent. Care was taken to break up the streptococcal chains well in the 10^{-1} dilution and counts proved to be very consistent for a given culture, the following being an average type of result: innumerable cols. and nearly complete hæmolysis on 10^{-5} plates, 130, 148 and 129 wide β hæmolytic colonies on the three 10^{-6} plates; and 13, 21 and 14 colonies on the 10^{-7} plates; giving a count of approximately 140 millions per c.c. Counts with different cultures varied from 80-220 millions per c.c. The actual count for each mouse experiment is given.

Attempts to Raise Virulence by Passage

Group C streptococci.—Small groups of mice were inoculated with 0.5 c.c. of falling dilutions of a series of strains from the required source and those strains selected which already had an A.L.D. of about 10^{-2}. These strains were then passaged by inoculation of mice intraperitoneally with 0.5 c.c. of blood or

serum broth culture and recovery of the strain from the heart blood. K64 was already highly virulent, the A.L.D. being usually between 10 and 100 organisms (as judged by colony counts). S34 was also fairly virulent and after two passages had an A.L.D. of about 100 to 1,000 organisms when injected without mucin and 10 to 100 with mucin. GM17 originally had an A.L.D. of about two million organisms but by the 17th passage the A.L.D. lay usually between one and 10 organisms. The term "usually" is inserted because with all strains, and particularly with highly virulent ones, the A.L.D. of successive subcultures was apt to vary widely, a subculture from a strain which was usually highly virulent sometimes proving to be a 100 or even a 1,000 times less virulent than expected. A number of therapeutic experiments were spoiled in this way, the control groups failing to behave as expected, with the result that no satisfactory conclusion could be reached regarding the treated mice.

Highly virulent variants of several other strains were obtained in the same way but not used for therapeutic experiments.

Group B strains.—Attempts to raise the virulence of group B strains in the same way were not possible, because these strains usually failed to kill mice even when 0.5 c.c. of undiluted culture was given and rarely killed at 10^{-1}. Attempts were therefore made to passage a series of strains by direct peritoneal passage, i.e., a mouse was inoculated intraperitoneally, the peritoneal cavity washed out with 0.5 to 1 c.c. of Ringer's solution on the next day and the washings inoculated into another mouse and so on. In some cases the peritoneal washings were first mixed with mucin. Some enhancement of virulence was thus obtained, more often when mucin was used, but in no case could the virulence be raised to anything approaching that required for therapeutic experiments. It is possible that the method finally used for group G strains might be successful with group B strains, but no opportunity of returning to these strains occurred.

Group G strains.—Freshly isolated strains of this kind were less virulent than group C strains but usually killed when given undiluted or at 10^{-1}. Direct peritoneal passage as described above for group B strains was carried through 17 to 23 generations respectively with three strains but, although some enhancement of virulence was obtained, no highly virulent variant was obtained. Variation of the procedure by incubation of the peritoneal washings in blood broth and inoculation of this into mice also failed. Highly virulent variants were, however, fairly easily obtained from the same three strains by inoculation of a series of mice with falling dilutions, culture in blood broth from the heart blood of the mouse which was killed by the smallest number of streptococci, inoculation of a further series of mice with a higher series of dilutions and so on. In this way five variant strains with an A.L.D. of eight to about 200 organisms were obtained within three or four passages.

Sulphanilamide Treatment

The mice used weighed about 20-30 g. Sulphanilamide was administered orally by means of a 1 c.c. syringe fitted with a needle of moderate size which had been cut off and ground smooth at the tip, the dose being placed directly into the œsophagus. Accidents were rare but any mouse which died within a few hours of dosing was discarded.

For dosing, the sulphanilamide was made up to a 10 per cent. suspension in 10 per cent. gum acacia. An initial dose of 20 mg., (i.e., 0.2 c.c. of 10 per cent. suspension) was given as soon as inoculation was finished, further doses of 10 mg. after 8, 16, 24 and 36 hours, and further doses of 20 mg. 48, 72, and 96 hours respectively after inoculation.

The mice showed marked inco-ordination of movement shortly after dosing and were very slow and sleepy but showed no other obvious symptoms and only one of numerous sulphanilamide controls died.

Post-mortem examination.—In the earlier experiments all dead mice were examined post-mortem, the heart blood being examined microscopically and, if negative, by culture. In the case of practically all mice which died during the first week after inoculation streptococci were obtained. Mice which died later were often negative. In later experiments only some 10 to 20 per cent. of dead mice were so examined.

Results

Group C Infections

Eight experiments were made with the group C streptococci. Details of four made with K64, S34 (with and without mucin) and with GM17 respectively are given in Table 1 and show that a high degree of protection was obtained.

In three other experiments made with K64, GM17 and S34 respectively the culture proved much less virulent than expected, and protection, though evident, was of a low order. In the other experiment the culture proved more virulent than expected, and, although protection was clearly of a high order, no end point was reached.

TABLE 1

Group C Infections

Controls, or Treated	Culture dilution	Strain, number of mice inoculated and number which survived (14 days)			
		K64	S34 (mucin)	S34	GM17 (mucin)
Controls	10^{-8}	5/5	5/5	—	2/5
"	10^{-7}	4/5	1/5	4/5	0/5
"	10^{-6}	3/5	1/5	3/5	0/5
"	10^{-5}	0/5	0/5	2/5	0/5
"	10^{-4}	0/5	0/5	0/5	0/5
"	10^{-3}	0/5	—	0/5	—
Treated	10^{-5}	—	16/20	—	—
"	10^{-4}	18/20	19/20	—	12/20
"	10^{-3}	20/20	3/20	12/20	1/20
"	10^{-2}	16/20	1/20	4/20	0/20
"	10^{-1}	12/20	—	1/20	—
Colony count per c.c. ...		200×10^6	215×10^6	140×10^6	80×10^6

TABLE 2

Group G Infections

Controls, or Treated	Culture dilution	Strain, number of mice inoculated and number which survived (14 days)		
		Price	18392 B	H
Controls	10^{-8}	4/10	7/10	—
"	10^{-7}	2/10	3/10	2/10
"	10^{-6}	0/5	0/5	2/5
"	10^{-5}	0/5	0/5	0/5
"	10^{-4}	0/5	0/5	0/5
Treated	10^{-6}	—	—	17/20
"	10^{-5}	18/20	17/20	15/20
"	10^{-4}	16/20	16/20	11/20
"	10^{-3}	13/20	7/20	12/19
"	10^{-2}	0/20	1/20	—
Colony count per c.c.		180×10^6	80×10^6	150×10^6

Group G Infections

Five experiments were made with the group G streptococci. Details of three made with Price, 18392 B and H respectively, are given in Table 2, and show

evidence of a moderate to high degree of protection. The other two experiments were made with variants of the same strains and gave similar results.

Discussion

As already stated, the object of these mouse experiments was to find out whether it was likely that sulphanilamide would be effective in the treatment of animal infections associated with streptococci of groups B, C and G. In the case of group C and group G the object was attained and gave reason to suppose that sulphanilamide would be effective in infections of the larger animals with these streptococci. The fact that in certain of the group C experiments only a minor degree of protection was obtained and that in others it appeared very high, does not detract from the significance of the results, because it is now common knowledge that in mouse experiments the exact degree of protection afforded is to a large extent a function of the virulence of the test culture. The great variation observed in the virulence for mice of subcultures made in exactly the same way from the same stock at intervals of a few days or weeks seems worthy of note.

Results have since been obtained with group C infections in equines which are in accord with those obtained in the mice. The treatment of infections of this kind was begun as soon as a suitable scale of dosage for equines had been ascertained (Stableforth, 1939) and the results have shown the considerable value of sulphanilamide treatment in certain of the more acute and common of these infections, in particular respiratory infections other than strangles (Hignett, 1939; Hignett and King, 1940; Hignett, 1940; Bazeley, 1940; Descazeau, Courtade and Rocq, 1939).

The relative value of the methods used in attempts to raise the virulence of strains required for test purposes deserves some mention. The method which gave the most satisfactory results was that which consisted essentially of the inoculation of a series of mice with falling dilutions, culture from the heart blood of the mouse which was killed by the smallest number of injected organisms, inoculation of a further series of mice with a higher series of dilutions, and so on until the desired degree of virulence was attained. This would appear to be the most effective way of selecting the more highly virulent variants. Direct transfer from peritoneum to peritoneum may be useful in the early stages with a strain which does not kill mice, but it failed to increase to any notable degree the virulence of three strains with which the method referred to above was quickly successful.

Summary

Evidence has been obtained in experiments on mice that oral treatment with sulphanilamide confers a high degree of protection against streptococci belonging to groups C and G respectively.

The group C strains were Lancefield's group strain (K64) and strains from cases of acute bovine mastitis and equine endometritis respectively.

The group G strains were all from dogs, one from a case of pneumonia and two from puppies which died soon after birth.

Attempts to render group B streptococci sufficiently virulent for mouse experiments were unsuccessful.

The value of various methods of raising virulence is discussed.

The latter part of the work, on streptococci of groups B and G, was carried out under a grant from the Agricultural Research Council, to whom we would express our indebtedness.

REFERENCES

Bazeley, P. L. (1940): *Aust. Vet. J. 16*, 187.
Descazeau, J., Courtade, R., and Rocq (1939): *Bull. Acad. Vet. France. 12*, 307.
Feinstone, W. H., quoted by Long, P. H., and Bliss, E. A. (1939): *The Clinical and Experimental Use of Sulfanilamide, Sulfapyridine and Allied Compounds.* Macmillan Co., New York.) p. 217.
Hignett, S. L. (1939): *Vet. Rec. 51*, 1245.
Hignett, S. L. (1940): *J.R.A.V.C. 12*, 3.
Hignett, S. L., and King, W. S. (1940): *Vet. J. 96*, 87.
Stableforth, A. W. (1938): *Vet. Rec. 50*, 1203.
Stableforth, A. W. (1939): *Vet. Rec. 51*, 1243.

CONGENITAL TUBERCULOSIS IN BOVINES

By W. M. McKAY, Ph.D., M.R.C.V.S.

UNTIL the demonstration of the infectious and inoculable character of tuberculosis, the recurring cases of the disease in families not unnaturally gave rise to the impression that heredity influenced its transmission to a very great extent.

The question of the transmission of the bacillus of tuberculosis from the parent to the offspring has caused some controversy, and, in spite of the experimental evidence of Gaertner, Grancher and Straus and others, of the transmission of *M. tuberculosis* by way of the placental circulation, some still maintain that all offspring of tuberculous parents are born free of disease.

Human cases of congenital infection appear to be very rare. Baldwin *et al.* (1927) stated that only about 60 authentic cases were on record and that all died soon after birth. The same authors stated that the only recognised type of inherited infection was by way of the placental circulation. Calmette (1923) admitted that fœtal infection by way of the placenta did occur in the human, but only rarely. In cattle, however, the same author stated that this mode of infection was more common. Bohmer (1934) reported that, of 300 fœtuses from tuberculous dams, nine were tuberculous, only one of which was from a dam with tuberculosis of the uterus.

Aguecia (1933) showed that *M. tuberculosis* can pass from the placenta to the fœtus without lesions of tuberculosis being present in the uterus or fœtal membranes.

Ehrlich (1935) propounded the theory that there may be a hereditary predisposition to tuberculosis in cattle and quoted the tuberculous histories of the progenies of a number of cows.

Rautman (1935) stated that hereditary disposition to tuberculosis in cattle is unimportant, but that there may be some predisposition because of faulty anatomical conformation. The dissemination of tuberculous infection by the male parent to the fœtus has never been demonstrated, and it can probably be accepted that the male does not play any part in congenital tuberculous infection.

McFadyean (1899) held the view that the fœtus was probably always affected by way of the bloodstream, the bacilli gaining access to the fœtal blood from a previously diseased placenta.

In the present investigation, which covers a period of two years, twelve cases of congenital infection were encountered amongst clinical cases of tuberculosis, and four others were met in slaughterhouses amongst animals which showed no evidence of disease during life and survived in good health until the age for slaughter at between two and three years old. Two cases in fœtuses were also met with.

Twelve clinical congenital cases represent approximately four per cent. of the annual clinical incidence of tuberculosis in Banffshire and tend to indicate an alarmingly high incidence of this type of infection.

Approximately 8,000 cattle are slaughtered annually in the abattoirs of Banffshire, and four congenital cases over a period of two years represent an annual incidence of .025 per cent. Assuming that sixteen cases (twelve clinical and four slaughterhouse) represent the true incidence for two years or eight per year, then with a population of 32,000 cattle of the critical age group, i.e., up to three years old, in Banffshire, it appears that the incidence is approximately .02 per cent.

The cases occurred in animals of from two months up to the age of three years and also in two six-month fœtuses. The age distribution was: two months old (1), three months old (1), five months old (1), six months old (1), ten months old (1), one year old (2), eighteen months old (3), two years old (3), two and a half years old (2), three years old (1). Since human congenital cases die soon after birth, there appears to be a considerable difference in this respect between the human and bovine, as three years in cattle would represent eighteen to twenty years old in the human.

Contrary to the experiences of Bohmer and Aguecia quoted above, in every case (8) where the post-mortem findings of the dam were known, infection of the uterus was evident.

In all of these eight cases acute generalised peritonitis with or without vegetative lesions was present and it is suggested that the route of infection was from the peritoneal cavity via the uterine tubules and so to the fœtus. In every case the progression of uterine infection, judged from the lessening in the severity of the lesions, was descending, that is, from the tubules towards the cervix.

In some cases the lesions were of a fleshy translucent character confined to the surface of the uterine mucous membrane, but in the others the lesions were of a caseous or caseo-calcareous nature involving in some the entire thickness of the uterine wall.

It would seem very unlikely that conception can occur once infection reaches the uterus, but pregnancy can continue to its normal conclusion when infection takes place after conception, probably even if the uterine lesions develop grossly.

The process of infection of the fœtus might well be as follows: On an actively progressive tuberculous dam becoming pregnant the physiological demands of the fœtal skeleton take precedence. Owing to the peculiar circumstances arising out of modern dairying, the cow to-day has to meet (1) the normal physiological mineral demands of her body, (2) the mineral demands of prolonged lactation, (3) of the fœtus, and in tuberculosis, (4) the pathological demands of

the tuberculous lesions. It is possible that these requirements bring about a negative maternal calcium balance and a consequent demineralisation of the lesions occurs. This apparently in some cases allows a liberation of bacilli into the blood or lymph stream with a consequent acceleration in the spread of the disease. Amongst other structures affected, the peritoneal cavity becomes the site of active peritonitis with free tubercle bacilli multiplying and assisted by peristaltic action circulating in the cavity. Some of these bacilli gain entrance to the uterine tubules via the ostium abdominale tubæ and then become static, first affecting the mucous membrane and later the walls of the uterus themselves, and the placental circulation carries the organisms into the fœtus. Whether the dam will live to complete her pregnancy appears to depend largely on the extent and distribution of the lesions present before conception took place. The great majority die of acute miliary infection either during pregnancy or, more commonly, shortly after parturition, the added strain of a fresh lactation hastening the conclusion.

In this connection, in the human, Baldwin *et al.* (1927) hold the diametrically opposite view that peritonitis may result in rare cases from the breaking down of uterine lesions and forcing the sealed ostium. This may be so in the human but in cattle the opposite appears to be true, since the uterine lesions are in most cases without doubt of more recent origin than the peritonitis and no caseation or breaking down had taken place in the uterus.

McFadyean (1899) discussed the probable origin of tuberculous peritonitis and expressed the view that it is probably always due to infection of the membrane by bacilli that reach it from a tuberculous ulcer of the bowel, a tuberculous mesenteric gland or a tuberculous pleurisy; the last two are considered more frequent than the first. This is supported by the illustrative cases hereafter described. Dealing with infection of the uterus and ovaries the same writer stated that the disease of these organs was not infrequent and was the result of centrifugal lymphatic extension from the peritoneum. He considered that primary tuberculous metritis was a possibility, infection being introduced during the act of copulation.

Tuberculosis of the uterus has not been encountered in the absence of tuberculous disease of the peritoneum. Further, tuberculous metritis was coexistent with peritonitis in at least 75 per cent. of cases where the latter structure was severely affected. Briefly, peritonitis can exist without metritis but the converse is probably very uncommon.

Unlike tuberculous spleen lesions in the human, horse, guineapig, pig or fowl, spleen lesions in the adult bovine are confined to the capsule of that organ only, lesions in the substance being regarded as conclusive evidence of congenital infection, but it has been found that they may be macroscopically absent from this organ in early fœtal infection. Spleen lesions were demonstrable in all the animals which had lived a separate existence but were macroscopically absent in one fœtus, the lesions in this one case being confined to the bronchial and mediastinal glands. The lack of lesions in the spleen of the adult bovine is probably explained by the lung lesions being so extensive before generalisation takes place that the animal dies before spleen lesions have a chance to develop, while in the congenital case the generalisation is established while the lungs are

functionally inactive and the pulmonary lesions few in number. Apart from the spleen no typically congenital lesions can be demonstrated and the character of the nodules themselves, while very often in the form of calcareous or caseous bullæ, does not differ from normal. In congenital disease, however, primary intestinal ulceration can sometimes be demonstrated and in this respect they differ from the accepted axiom in tuberculosis of a reinfection before ulceration, unless an endogenous reinfection in utero is accepted.

Cases of congenital infection react severely to the tuberculin test when tested soon after birth. It is probable that the preponderance of tuberculomas are found in congenital infection, meningitis without actual brain lesions are common and of the sixteen cases met with nine showed brain or meningeal lesions or both, while these structures were not examined in five cases so that it might be stated that this type of lesion in young animals is almost certainly indicative of congenital infection. Details of each of the sixteen cases would be largely repetition, so that only the more interesting autopsy findings will be given in detail.

CASE A

Dam. Five-year-old cow.

Autopsy.—Extensive calcareous lesions throughout mesenteric glands. Acute diffuse peritonitis with old caseous grape lesions. Crater ulceration of mucous membrane of small intestine. Caseous areas in hepatic gland and in substance of liver. Cortical lesions in left kidney. Grape lesions of a translucent character on mucous lining of uterus. Nodular caseous lesions in left posterior quarter of udder. Acute diffuse pleurisy, old caseous lesions in both lungs with superimposed miliary lesions. Small pea-like caseous lesions in bronchial, mediastinal and retropharyngeal lymph glands.

Six months old fœtus.—Small rounded shot-like caseous lesions in substance of spleen and similar lesions in substance of liver.

CASE B

Seven-year-old red horned cow.

Acute fibrinous peritonitis. Caseous areas in both supra-mammary lymph glands, small caseous nodules in both posterior quarters of udder. Acute lesions on peritoneal covering of intestines. Caseous lesions in portal, hepatic and mesenteric glands. Gross tuberculous ulceration of intestinal mucosa. Caseous areas in wall of uterus. Acute diffuse pleurisy. Miliary lesions in both lungs with older caseous lesions. Calcareous lesions in bronchial and mediastinal lymph glands. Large cortical lesions in right kidney, small scattered lesions in cortex of left kidney.

Six months old fœtus.—Small calcareous lesions in bronchial and mediastinal lymph glands. No other macroscopic lesions found.

CASE C

This case was known from birth to maturity at two years old, when it was sent for slaughter in the normal way. The mother was destroyed a few days after delivery and post-mortem examination showed the uterus to be affected with tuberculosis. The calf was immediately tuberculin tested and gave a severe reaction to the intradermal test. No evidence of tuberculosis was noted during the next two years but generalised infection was found when slaughtered.

Dam. Six-year-old black polled cow.

Acute diffuse peritonitis with old grape lesions. Acute areas on spleen capsule, liver capsule and omentum. Large abscess in liver. Ulcerative enteritis, caseous lesions in wall of uterus. Cortical lesions in both kidneys. Caseous areas in both posterior quarters of udder. Caseous lesions in mesenteric, iliac and supra-mammary lymph glands. Acute diffuse pleurisy and pericarditis, caseous areas in both lungs and in bronchial and mediastinal and in both prescapular lymph glands.

Offspring. Twenty-eight months old heifer.

This animal had not shown any indication of disease while alive.

Post-mortem.—Scattered caseous grape lesions on pleura. Caseous areas scattered throughout both lungs, caseous lesions in retropharyngeal, bronchial, mediastinal and mesenteric lymph glands. Caseous lesions on peritoneum, calcareous nodules in substance of spleen and substance of liver, cortical lesions in both kidney and renal lymph glands.

CASE D

Seven-year-old red and white cow.

Dam.—Milk and sputum both showed numerous tubercle bacilli on microscopical examination. Tuberculous lesions in udder, capsule of spleen and liver, cortical lesions in kidneys. Acute and caseous lesions on peritoneum and pleura. Caseous lesions in wall of uterus and in hepatic, portal, bronchial, mediastinal and right retropharyngeal lymph glands. Caseous areas scattered throughout substance of lungs.

Offspring. Three months old heifer calf.

This animal showed clinical evidence of disease, was coughing and losing condition.

Post-mortem.—Pin-head calcareous lesions in substance of spleen and liver. Calcareous lesions in hepatic, bronchial and mediastinal glands. Extensive caseation of both lungs. Multiple cortical lesions in both kidneys. Mesenteric glands enlarged but no macroscopic lesions noted. Gastric glands caseous.

CASE E

This was a two-month-old calf born with opacity of both corneas with resultant blindness. It had a very unsatisfactory history and had been losing condition since birth and had become " stupid " in its behaviour about two weeks before slaughter. It had a good appetite, no cough had been noted but auscultation of the chest indicated pulmonary disease. The precrural and prescapular glands were prominent and indurated.

Autopsy.—Cervical lymphatic chain enlarged indurated and caseous. Retropharyngeal glands enlarged to size of egg indurated and caseous, prescapular, submaxillary, precural and popliteal lymph glands enlarged and caseous. Fibrocaseous lesion in right testicle. Acute diffuse peritonitis, numerous small pea-sized calcareous lesions in substance of spleen and liver. Portal and hepatic glands very enlarged and caseous. Sparse barley-sized caseous lesions in cortex of both kidneys and renal lymph glands. The adrenal glands very enlarged indurated and congested. The mesenteric glands were the size of duck eggs and entirely caseous. Peyer's patches showed shot-like caseous nodules. One crater ulcer in bowel mucosa. Grape lesions on pericardium and some fluid in sac. Bronchial and mediastinal glands enlarged and caseous. Very extensive caseous

myocarditis of left ventricle, valve of right ventricle and wall of right ventricle. Grape lesions on right auricle. Grape lesions on pleura. Few caseous bullæ in both lungs. The brain was very extensively affected, there were pea-sized caseous lesions on surface of medulla easily shelled out, with numerous pedunculated caseous lesions round the cerebrum, small pea-sized encapulated lesions in cerebral cortex. Pronounced miliary lesions on brain meninges. Caseation of gastric, iliac and prostate glands. Gross infection of both eyes.

Dam.—The mother of this calf was re-examined in view of the above findings. She was eleven years old and had shown no sign of œstrus since calving two months before. She was thinnish and dry in the hair but the skin was loose. She was eating well and it was stated by the owner that she was in her normal condition for the previous nine years, i.e., since purchase. No cough had been noted but coughing must have occurred occasionally, since dried sputum was obtained from the wall in front of her head and proved on microscopical examination to contain numerous *M. tuberculosis.* She was consequently slaughtered.

Autopsy.—Acute diffuse peritonitis with multiple sessile lesions on peritoneal coverings of stomach and abdominal wall. Multiple lesions on spleen and liver capsules. Grey fibrinous lesions on omentum. Mesenteric chain prominent but no obvious lesions. Diffuse lesion at anterior pole of right kidney and one pin-head cortical lesion. Small fleshy translucent lesions on mucous membrane of uterus. Gross pleurisy with multiple "grape" lesions. Calcareous areas in bronchial and mediastinal glands. Multiple old lesions in both lungs with some bean-sized cavities. Some pericarditis.

Discussion

Tuberculous disease of the female genitalia is a common occurrence and may result in pregnant females in the transmission of the disease to the offspring. The incidence of congenital tuberculosis appears to be about .025 per cent. of calves born and about 4 per cent. of annual clinical cases.

The primary cause may be an activation of extensive tuberculous lesions on the establishment of pregnancy and the setting up of acute peritonitis with spread to the uterus via the ostium abdominale tubæ and so to the fœtus. Seventy-five per cent. of cases showing extensive peritonitis exhibited tuberculous metritis. Conception is unlikely if metritis is established but may continue successfully if the disease occurs after conception. Since the extension and severity of the condition is descending, ovulation is probably impeded by blocking of the ovarian tubules and consequent inhibition of conception. This would account for the disparity between the high incidence of tuberculous metritis and the low incidence of congenital disease.

Summary

The incidence of congenital tuberculosis in bovines is discussed from data available from clinical and abattoir cases of tuberculosis. The ages of sixteen cases and of two fœtuses are given and it is shown that the bovine with congenital infection can survive up to three years. The probable ætiology of congenital infection is set forth.

The lesions in congenital tuberculosis are discussed and the post-mortem findings of dam and offspring are given in detail in five cases.

REFERENCES

Aguecia, A. (1933): *Pathologica, 25,* 413.
Baldwin, Petroff and Gardner (1927): *Bacteriology, Pathology and Laboratory Diagnosis of Tuberculosis.*
Bohmer, G. (1934): *Inaug. Diss. Berlin.*
Calmett, A. (1923): *Tuberculous Bacillus Infection and Tuberculosis in Man and Animals.*
Ehrlich, C. (1935): *Z. Zucht. B., 10,* 1.
McFadyean, J. (1899): *J. Comp. Path. and Therap.*
Rautmen, H. (1935): *Disch. Tierarzth, Wschr., 43,* 577.

SOME ANIMAL CASUALTIES BY ENEMY ACTION

By W. F. BARTON, B.Sc., M.R.C.V.S.,

Brentwood

More than three years of war have passed and communiqués quoting damage by enemy action have become almost commonplace. Judging from personal experience there must have been many casualties amongst the animals of this country and veterinary surgeons must have many experiences which it would be well to relate. In spite of this, little or nothing has been published of experiences in the field. No doubt there are records available from the experimental stations, but it would be regretted if these were the only records handed on to posterity.

Therefore, I set down one or two incidents culled from a varied and, at times, hectic experience, in the hope that I may set the ball rolling and so encourage colleagues to do likewise.

Case I.—The subject was a half-bred Shire gelding aged twelve years. It was grazing peacefully in a field until the arrival of a hit-and-run air raider. Four bombs were dropped. The nearest bomb was of 500 lb. and it fell at approximately 200 yards distance from the horse.

The owner saw the animal within 15 minutes. His description was as follows: The animal was standing, blowing and sweating. The muscles appeared to be in spasm and the horse could hardly move. It appeared to be stuck to the ground. It took over half an hour to get it to the stable, a distance of 150 yards.

I saw the horse about one hour after the bomb incident. The above description was substantially correct. There was a general appearance which somewhat simulated tetanus with laminitis. The neck was very rigid, blowing respiration and widely dilated nostrils. There was no temperature reaction. One could not raise the fore feet. When one attempted to turn the animal it would almost fall over, and it turned rigidly like a boat. The pupils were dilated, pulse fast and there appeared to be a condition of fright or fear.

The bombing occurred in the early afternoon. Chloral was given and by evening the animal was easier, but not feeding. Next day there was considerable improvement: it was eating, and moved and walked much better. In three or four days the animal appeared to be all right, and it was turned out. On the eighth day the symptoms returned, and this time the eyesight was affected, and in two or three days it was totally blind. The slightest push would have caused the horse to fall over. Throughout the illness it never lay down. As the con-

dition gradually became worse it was decided to destroy the animal. A post-mortem was made but nothing abnormal was noted.

Case II.—Subject: A red Shorthorn cow, one of a herd of twenty. They were lying down in a field at night when a stick of small bombs was dropped. Three dropped in the field. Seven beasts were killed. The Shorthorn was wounded in the right chest. Three ribs were fractured and through the hole we could see the lung. Several pieces of bone were easily removed. There was considerable shock, rapid blowing respiration and, as it was summer, the wound was much troubled by flies. One could hear air going in and out of the wound. The cow was dry, near calving, and it kept feeding, and later it calved normally. The wound was dressed with Dettol and carbolic oil. It took three or four months to heal. There was periodic sloughing of bone particles and other tissue of the chest wall. Recovery from this extensive chest injury was ultimately complete, except for local scar.

Case III.—Subject: Shire gelding. Bombed in a field at night. In the morning was found to be acutely lame, so that it could not put its foot to the ground. The hoof was damaged on the toe area, midway between the coronet and ground. There was a hard metallic object in the wound, which proved to be a piece of "shrapnel," 1 in. by ½ in., and wedge shaped. The thick part of the wedge was embedded in the sensitive structures.

The foreign body was extracted under general anæsthesia and the wound dressed. Progress was uninterrupted and in a week the horse was walking sound. The dressing used was acriflavine.

Case IV.—Subject: A Suffolk gelding. Bombed in a field. It was cut completely in half. The forequarters and head and neck looked as if nothing had happened to the carcase but in spite of diligent search no trace of the hind-quarters and hind part of the trunk could be found.

The above are examples of some of the unusual conditions with which we may be called upon to deal in these days of total war. I have met with many instances of bomb damage. There is no direct rule as to the effects produced by other than direct hits. It is strange that often those that are injured are not the closest to the offending missile.

TORSION OF THE UTERUS

By RICHARD HUDSON, F.R.C.V.S.
Retford

THE subject was a Dairy Shorthorn heifer. She was bought for 63 guineas two days before I saw her and was then fully prepared for calving. She was uneasy during the day following purchase but never attempted to calve, and at night the owner thought she needed attention.

On examining her I found a twist across the vagina through which I could pass two fingers. Two folds, one above and one below, were present in the vaginal wall and appeared to pass straight to the twist. These gave no indication of the direction of the twist but in the twist itself the folds passed from right to left in a clockwise direction. As there were no facilities for operating in the

dark and no place roomy enough to cast her, operation was postponed until next morning.

On examining her I found no further change in the twist, so the heifer was cast with sidelines but not tied up tightly, as I think that the abdomen may be compressed so as to prevent the body of the cow from rolling round the womb. Before rolling I inserted my hand to make sure of the direction of the folds and then rolled her in their direction, examining after each roll to find what had happened. After three rolls nothing had happened, so she was given a roll in the opposite direction. This tightened up the twist so much that I had to use force to insert two fingers, so the rolling was reversed, and after twice rolling the twist disappeared. The os was dilated to admit two fingers (about 1½ inches). She was given Liq. Ext. Ergot ℥j and left to dilate. During the day she made no effort to calve but at night had dilated sufficiently for me to bring the feet and head into the passage, so I decided to risk delivery of the calf. The os still remained like a tight band and during delivery I tried to stretch it by forcing it away from the fœtus. Delivery proceeded slowly and when the head reached the vulva further difficulty was encountered owing to unrelaxed conditions. Lubrication, time and stretching, however, enabled me to deliver the calf, a very large one and dead.

Examining for injury I found a tear about 6 inches long in the wall of the vagina and the right vaginal artery was bleeding furiously. It was held by the fingers until artery forceps were obtained from the car and applied, checking the hæmorrhage. About half a gallon of blood was removed as one large clot, in addition to the amount which had escaped, so she would soon have bled to death if the forceps had not been applied.

The following morning she was fairly well but had not cleansed. Pessaries of iodoform and salol were inserted and sulphanilamide ℥iij was administered and continued daily. I hesitated to interfere with the placenta, for fear of disturbing the forceps. Three days later I was able to remove it and the forceps came away during the operation without any further hæmorrhage.

The vagina was douched with weak antiseptic solution every two or three days and the heifer showed no signs of sepsis. She is now milking very well.

Remarks

I lost two cases last year owing to laceration of the os during delivery of the calf, even though I had waited several hours for dilation to take place. It is a question how long one should wait after removal of the twist. Some cases can be delivered almost at once, others dilate very slowly, and some may contract or become more rigid. Perhaps, owing to the calf being dead, labour pains are in abeyance.

Tears of the vaginal wall with rupture of the artery are very serious, and one should always be prepared to apply forceps, for such cases will be almost sure to bleed to death. Also hæmorrhage may occur about seven to ten days later, when the slough separates, and a further application of the forceps is necessary.

Abstract of Current Literature

THERAPEUTIC CONTROL OF LACTATION*

By LOUIS A. KLEIN,
University of Pennsylvania

LITTLE or no increase in milk production, except perhaps temporarily, can be expected from the administration of drugs or other therapeutic agents when the mammary gland is operating at its maximum capacity. There are times, however, when the milk secretion of a cow is below the optimum for the individual concerned, or when that of the mare or bitch or females of other species is inadequate for the nourishment of the young. In such cases, therapeutic measures may be indicated, and these are likely to be most effective if based upon the physiology of milk secretion.

All attempts to demonstrate the presence of secretory nerves in the mammary gland have been unsuccessful. The secretory nerve stimulants, pilocarpine, physostigmine and arecoline, and the secretory nerve depressant, atropine, have no direct effect on milk secretion. For many years, black sulphide of antimony, sulphurated antimony, and sulphur, were prescribed to increase milk secretion in the cow, but pharmacological studies have failed to yield any evidence that they increase milk production, and the reputation they acquired as galactagogues was evidently due to the fact that they were usually combined with stomachics.

Immediately following recovery from an exhausting disease, or as a result of improper or insufficient feed, milk production may be below normal in quantity because the digestive secretions are deficient or weak and the appetite is poor. In such cases, the administration of stomachics with suitable feeding is effective in increasing milk production. Digestive disturbances in the cow may be attended by the development of an "off" flavour in the milk. In these cases, the saline stomachics have been found useful.

If the heart action is weak, vasomotor tone low, and the circulation slow and sluggish, circulatory stimulants may be helpful.

In experiments on cows, anterior pituitary extract was found to be more effective than lactogen,† indicating that not only that hormone but also other anterior pituitary hormones (thyrotropin and adrenotropin) have an effect on milk production. Subcutaneous injections of anterior pituitary extract, 10 c.c. every other day, over a period of 22 days, caused an increase of 16 per cent. in the milk production of four cows in which production had begun to decline, while injections of a preparation of lactogen on a similar schedule caused an increase of only 5 per cent. in the quantity of milk produced by four other cows in the same stage of lactation. In the late stage of lactation, when the cow is "going dry," little or no increase of milk production is likely to follow the injection of anterior pituitary extract, because by that time many of the secretory cells in the alveoli are inactive, having undergone degeneration and atrophy. Nor should any increase be expected if the injections are made when milk production is at the maximum level, since an excess of hormones cannot increase the secretion of milk beyond the inherited capacity of the individual cow.

* *University of Pennsylvania Bulletin*, Vol. xliii, 1942-3.
† Lactogen is one of the anterior pituitary hormones.

The usual doses of anterior pituitary extract, subcutaneously, are as follows: horse and ox, 5 to 10 c.c.; sheep and swine, 2 to 4 c.c.; dog and cat, ½ to 1 c.c. Anterior pituitary extract also contains the gonadotropic hormone and is therefore contraindicated for pregnant animals. When non-pregnant animals are treated, observation should be made for excessive œstrogenic action. Sometimes it produces a mild form of nymphomania.

The follicle-stimulating and luteinising action of the gonadotropic hormone, i.e., anterior pituitary, on the ovaries leads to the secretion of œstrogen and progestin. Œstrogen stimulates the development of the duct system of the mammary gland and progestin the development of the alveoli, not by direct action but by causing mammary-growth hormones with corresponding actions to be secreted by the anterior pituitary. These facts suggested that anterior pituitary extract might have a beneficial effect when a cow "freshened" with one quarter smaller than the corresponding quarter on the other side of the udder. Only two such cases have been treated up to this time.

The first case treated was in a first-calf heifer which "freshened" with the left hind quarter about two-thirds the size of the right hind quarter and it did not increase in size during the succeeding two weeks. At this time, two 5 c.c. doses of anterior pituitary extract were injected subcutaneously 24 hours apart. The day after the second dose there was a profuse mucus discharge from the genital tract. One week later the left hind quarter was of the same size as the right. There was also a slight increase in the total daily milk production but no more than is usually normal at this stage of lactation. The quantity of milk produced by each of the individual quarters was not determined either before or after treatment.

The second case, which was in a cow which had "freshened" the second time, did not respond to treatment.

Thyroxin, obtained from the thyroid gland or prepared synthetically, increases milk secretion in cows in declining lactation and also increases the per cent. of solids in the milk, especially the butter fat. These effects are attributed to the action of thyroxin in increasing the quantity of milk precursors by stimulating the metabolic rate and increasing the quantity of blood passing through the udder by stimulating cardiac action. An increase in the quantity of milk precursors supplied to the udder would depend upon the ingestion of a sufficient quantity of feed to furnish the nutrients required by the increased general metabolism. Doses of 10 to 15 mg. daily for three successive days, injected subcutaneously in alkaline solution, caused an increase of 10 to 20 per cent. in milk production, a marked increase in the per cent. of fat and a slight increase in the solids-not-fat. The maximum increase in milk production was usually attained in five to eight days but secretion continued at an elevated level for 10 to 14 days. Cows in which lactation has recently begun to decline give the most pronounced response. When production is at the maximum level or near the end of the lactation period the effect is negative. Daily doses of 2 ozs. of desiccated thyroid per os over a period of eight weeks also increased milk secretion but to a less extent. A slight loss in weight usually attended the administration of either thyroxin or the dried gland.* Similar results were

* Similar experiments are now in progress in Great Britain with a view to determining whether thyroxin and iodine compounds are of value in increasing milk yields under practical conditions.

obtained in goats. The thyrotropic hormone secreted by the anterior pituitary stimulates the thyroid gland and thus influences the production of thyroxin.

It is sometimes necessary to reduce or inhibit milk secretion in mares and bitches when lactation persists after the death or removal of the offspring; also in some bitches at estrum or later (pseudo-pregnancy). A number of drugs have been prescribed for this purpose, among them potassium iodide, belladonna, camphor, quinine and alum. In experiments with potassium iodide, it was found that when daily doses of 45 to 90 gr. (3 to 6 gm.) were administered to cows, goats and asses, the milk secretion was at first somewhat increased and then rapidly reduced. As before mentioned, atropine does not depress milk secretion but it is possible the local analgesic action of this alkaloid may cause belladonna to afford some relief to the pain resulting from an over-distended mammary gland if applied in ointment with a lard or lanolin base and well rubbed in. The use of the other drugs mentioned for the purpose under discussion is purely empirical and there is considerable difference of opinion as to their actual value.

It was learned some time ago, in experiments on laboratory animals, that milk secretion can be inhibited by œstrogens, the female sex-hormone, and more recently it has been used clinically to terminate lactation in woman. Apparently, it has not been used clinically to any extent for this purpose on the domestic animals.

In experiments on cows with œstrogens, milk secretion was decreased when a sufficient dose was administered but some of the cows aborted and others developed nymphomania or were difficult to get with calf.

Testosterone, the male sex-hormone, having been found to inhibit milk secretion in laboratory animals, has been used clinically in the form of the propionate to terminate lactation in woman, but when injected subcutaneously or intramuscularly it has a tendency to produce masculinising effects (deepening of the voice, hairiness and amenorrhœa). These effects were not observed when testosterone or its propionate was applied to the mammary gland in ointment.

Apparently the male sex-hormone has been employed rarely, if at all, to reduce milk secretion in the domestic animals, but its use in selected cases on the basis of present knowledge would seem to be justified. Preparations of the male sex-hormone, however, are expensive.

Obituary

PROF. JAMES FERGUSON CRAIG, M.A., F.R.C.V.S.

THE news of the untimely death of Professor J. F. Craig was received with profound regret by the Veterinary Profession and the Agricultural Community throughout the length and breadth of these islands. He was taken suddenly ill on January 17 and after a few days passed away despite the best medical skill.

When this news has travelled abroad his passing will be mourned in many lands by his former students, who, during their college days, held him in the highest esteem and admiration.

His unexpected death will be felt keenly by the members of Council of the Royal College of Veterinary Surgeons—meetings of which he attended only a few days before his death, when he appeared to be in his usual good health and spirits. It was the writer's privilege to have been in close contact with him during the days of those meetings and to have accompanied him on his homeward journey, but no sign of approaching illness was apparent and his conversation was, as of old, sometimes deeply immersed in profound technical matters and at other times jocular, of a lighter vein, mingled with entertaining reminiscences.

Professor Craig was born at Hardgate, Dumbartonshire; receiving his primary education at a local school, he gained a county scholarship and entered Glasgow University, where he graduated M.A. in 1898. Choosing the Veterinary Profession as his calling, he commenced his studies at the Glasgow Veterinary College, where the first two years of the curriculum were spent. He then proceeded to the Royal Veterinary College, London, where he qualified in 1902. His curriculum was brilliant throughout. He obtained honours in all his professional examinations, and the other distinctions and medals gained are too numerous to specify. On qualifying he was appointed Tutor in Medicine at the London College and in 1903 came to Ireland on being appointed to the chair of Anatomy and Histology in the Veterinary College, Dublin. In 1908 he succeeded Professor Wooldridge as Professor of Medicine and Parasitology, and in 1917, following the death of Professor Mettam, he was appointed to the Principalship of the College—a position which he held with dignity and distinction until 1935, when he was appointed to the Prescott Chair of Pathology in the University of Liverpool, and soon after the later appointment he became Acting Director of the Veterinary Faculty of that University in succession to Professor Share-Jones.

His sojourn in the Dublin College embraced the greater part of his professional life and it can be justly claimed that the success of that institution was in no small measure due to his wise guidance and well-balanced judgment. Perhaps his outstanding achievement during that period was his sponsoring of the Irish Veterinary Surgeon's Bill, which led to the establishment of the Irish Veterinary Council, and as a fitting climax to this work the Council of the Royal College of Veterinary Surgeons unanimously elected him President for the year in which the Agreement regarding that Act was ratified.

When he decided to leave Ireland the news of his impending departure was received with profound regret throughout the length and breadth of that country, north and south, and this was expressed in the form of a handsome presentation and a farewell dinner, which was one of the best attended functions ever held by the Irish members of the profession. Truly it can be said that not only did he leave behind him in Ireland many sincere friends, but he also left his indelible mark in the advancement of veterinary science in that country, as indicated by his contributions to veterinary literature, which has been enriched by his many scientific and clinical articles.

Perhaps his most notable contributions were those on contagious abortion, and plant poisoning of various kinds. He also contributed articles to Wooldridge's Encyclopædia and Wallis Hoare's Veterinary Medicine, and he edited and revised the third and fourth editions of Fleming's Veterinary Obstetrics.

He has acted as External Examiner in Anatomy for the B.Sc. degree in

the University of London; for the B.V.Sc. degree in the University of Liverpool; and also for the B.Sc. degree in Agriculture in Queen's University, Belfast. He was a member of the Royal Irish Academy; a member of the Council of the Royal Zoological Society of Ireland and a Past-President of the Veterinary Medical Association of Ireland.

In 1929 Professor Craig was the recipient of the greatest honour which the Veterinary Profession could bestow upon a member when he was elected President of the Royal College of Veterinary Surgeons. In deference to the wishes of his confrères in Ireland he obtained the consent of the Council to hold the Annual Meeting and Dinner of the Royal College in Dublin during his year of office. The large numbers who were present at that function will remember the dignity and distinction with which Professor Craig occupied the Presidential chair on that occasion.

In 1931 Professor Craig was selected by the Council of the Royal College of Veterinary Surgeons as a worthy recipient of the John Henry Steel Medal in recognition of scientific and literary work of special merit, and in 1936 the Council conferred upon him the Fellowship Diploma on account of his special eminence in the profession.

In 1934 yet another high honour awaited him, when he was elected President of the National Veterinary Medical Association of Great Britain and Ireland, and very many members of the profession will have happy recollections of the Annual Meeting of his year of office in Belfast, when he and his gracious wife gave of their hospitality and generosity in a manner never to be forgotten.

Professor Craig was a man possessed of unusual calmness, of unfailing courtesy and generosity, and his well-balanced judgment proved on many occasions to be a pillar of strength in guiding the destinies of the Veterinary Profession in both Great Britain and Ireland. Although his disposition was calm, reserved and perhaps, at times, undemonstrative to a fault, yet hidden beneath the surface was a highly sensitive and retiring nature which might have been a handicap to other men of less outstanding ability and personality. Only those who knew him long and intimately could possibly detect the true significance of the human touch and kindness of heart which lay in the depth. This hidden part of his nature was always clearly revealed to those privileged to some acquaintance with his private life, particularly by his devotion to his wife and only son, and one has only to recall his human emotions on the death of his infant son many years ago to realise that, although his mentality was that of a giant, his heart was but that of a child.

As a teacher, Professor Craig had few equals, his painstaking methods, his untiring devotion to his students and the soundness and depth of his knowledge engendered a degree of respect amongst his students rarely equalled by any man.

It was as a colleague and a Principal that the writer knew him best, and in that capacity he was the embodiment of uprightness, fairness, geniality, and, at the same time, perseverance. Never a harsh nor angry word crossed his lips. His genial, unassuming disposition and his native tact caused the happiest relations between himself and the staff. There was in the depth of his character that indescribable something which drew him closer and closer to those associated with him, and the writer, being one who was privileged to experience 27 years

of this personal contact, cannot accept the shock of his sudden passing as otherwise than an irreparable and irretrievable loss which cannot be assuaged.

The story of his life would be incomplete without a reference to the help and comfort afforded to him by his devoted wife, who survives him and who was his untiring helpmate for nearly his entire professional life. She was the youngest daughter of the late Adam Scott, of Dublin.

His only surviving child, Dr. Kenneth Craig, B.A., M.B., who is now serving with the Forces in Africa, was a prominent member of the Irish International Hockey Team for a number of years and rarely did his father miss being present at International matches in which Kenneth took part.

For Mrs. Craig and for his son, who is unfortunately abroad, the deepest and sincerest sympathy is felt throughout the profession.

Jim Craig, as he was affectionately known by the profession and his intimate friends, has gone from us for ever, but his memory will survive, and after the passing of this generation his work and achievements shall remain as an everlasting memorial of his devotion and self-sacrifice for the profession which he loved so dearly and to which he was " faithful unto death."

T. G. Browne.

HEDLEY GOLLEDGE, F.R.C.V.S.,

Dr. Med. Vet. (Zür.)

Dr. Hedley Charles Darys Golledge died in December, 1942, at the Yeatman Hospital, Sherborne, following an operation. He was 53 years of age. Born at Sherborne, he was the second son of the late Major C. Hedworth Golledge. He was educated at Dean Close School, Cheltenham, and later proceeded to the R.V.C., London, qualifying M.R.C.V.S. in 1910. In 1911 he joined the staff of the Ministry of Agriculture. In 1921 he left the Ministry and entered into private practice at Yeovil. Keen, able and conscientious, he built up a large practice and a reputation for professional skill which extended far beyond the town of Yeovil. He held professional appointments under the Ministry of Agriculture, the Borough of Yeovil, the Cattistock Hunt, and numerous other bodies.

Throughout his life he took every opportunity to add to his professional knowledge. In 1917 he took the Fellowship of the R.C.V.S. and in 1931 he proceeded to Zürich in order to study for a degree of the University of that town. This he obtained following extensive research work in Pathology. His life is a great example to all, for here was a man who might have been content with the care and toil of a busy practice but still had the urge to go forward and endeavour to add to the store of scientific knowledge. He was not the man to ask for or await the award of some scholarship in order to attain his ambition, but one who, having set the goal, attained that goal by his own efforts. His reward was that he succeeded, and thereby brought added prestige, not only to himself, but also to his profession. Golledge was of a type which is all too rare in these days of scholarships, grants and ready-made education.

A profession can ill afford to lose such sturdy and self-reliant men, who, seeing the need, make the opportunity and rely on their own resources.

He took a keen and active interest in his local Veterinary Society and served for many years on the Council of the N.V.M.A.

We extend our sympathy to Mrs. Golledge and family in their sad loss. It will be a comfort to them to know how deeply he was appreciated, as the following extract from a letter penned by two of his clients will show:

"By the grace of God, a man of great skill and high ideals, with a sterling integrity of purpose, an unfailing courtesy and kindness to all with whom he came in contact. An honour to his profession."

Would that we could all earn such an epitaph.

News

THE Secretary of State for the Colonies has approved a recommendation of the Colonial Advisory Council of Agriculture and Animal Health that its functions should be extended to include forestry. The Council will accordingly in future be known as the Colonial Advisory Council of Agriculture, Animal Health, and Forestry. Additional members will be appointed to the Council to advise on forestry matters, and a Forestry Committee will shortly be set up, parallel to the existing committees of the Council which deal with Agriculture and Animal Health. The Duke of Devonshire, as successor to Mr. Harold Macmillan, Parliamentary Under Secretary of State for the Colonies, has assumed Chairmanship of this Council; the Vice-Chairman is Mr. G. L. M. Clauson, C.M.G., O.B.E., Assistant Under Secretary of State.

Publishers' Notices

All communications should be addressed to 7 and 8, Henrietta Street, Covent Garden, London, W.C.2. Telephone: Temple Bar 8568. Telegrams: "Baillière Phone, London."

Letters for the Journal, literary contributions, reports, notices, books for review, exchanges, new instruments or materials, and all matter for publication (except advertisements) should be addressed to the Editor.

Copy of advertisements should be in the hands of the publishers—Baillière, Tindall and Cox—not later than the 1st of the month, if proof is required.

Binding Cases for Volume 98 and any other previous volumes can be obtained from the publishers. Price 3s. 9d. post free.

Annual Subscription, 25s. ($6.00 U.S.A. currency), post free.